

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
SODIUM CHLORITE (includes also all relevant CHLORINE DIOXIDE data)

Chemical Code # 2148, Tolerance # 50288

SB 950 # 318

1/25/01

Revised: 9/10/01

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, inadequate study, no adverse effect indicated
Chronic toxicity, dog:	Data gap, no studies on file
Oncogenicity, rat:	Data gap, no studies on file
Oncogenicity, mouse:	Data gap, no studies on file
Reproduction, rat:	Data gap, no studies on file
Teratology, rat:	Data gap, no studies on file
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, possible adverse effects
Chromosome effects:	No data gap, possible adverse effects
DNA damage:	No data gap, no adverse effects
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 130837 (Document No. 50037-018) containing relevant, reviewable data were examined. This includes all records containing required study types for Chemical Code # 2148 (sodium chlorite) or Chemical Code # 2053 (chlorine dioxide) as of 1/16/01.

In the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: t20010910.doc

Revised by C. Aldous, 9/10/01

NOTE: 1-LINERS BELOW REPRESENT TWO REGISTERED ACTIVE INGREDIENTS:

Chlorine dioxide	Chemical Code 2053	DPN: 50037	and
Sodium chlorite	Chemical Code 2148	DPN: 50288	

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

50288-003 954407 (accompanied by a cover letter by Prof. H. B. Haag, Medical College of Virginia, Feb. 7, 1949). This was a chronic study with typically 7 rats/sex/group at drinking water dose levels of 0, 1, 2, 4, 8, 100, or 1000 ppm sodium chlorite. Additional control groups of 7 males or females were given sodium chloride at ionic concentrations equivalent to 1000 ppm sodium chlorite. Water consumption was markedly reduced in 100 ppm females and in 1000 ppm males and females given sodium chlorite. The two highest dose groups of males had kidney lesions (distended glomerular capsules and tubules filled with pink-staining material). Since the latter was even more pronounced in the sodium chloride control group, it was considered to be a result of heavy salt loading. This study does not fill guideline chronic study requirements, nor does it provide significant information about oncogenicity. No worksheet is warranted. Aldous, 1/16/01.

CHRONIC TOXICITY, DOG

No studies submitted.

ONCOGENICITY, RAT

No studies submitted.

ONCOGENICITY, MOUSE

No studies submitted.

REPRODUCTION, RAT

No studies submitted.

TERATOLOGY, RAT

No studies submitted.

TERATOLOGY, RABBIT

****50288-058 115606** Irvine, L. F. H., "Sodium chlorite: rabbit teratology study (drinking water administration)" Toxicol Laboratories Limited, Herfordshire, 9/21/90. Laboratory Project ID: CMA/3/R. Sixteen or 17 NZW does/group were dosed in drinking water with 0, 200, 600, or 1200 ppm sodium chlorite (80.58% purity, dosing levels adjusted for purity) on gestation days 7-19 in a standard developmental toxicity study. Maternal NOEL = 200 ppm (13.0 mg/kg/day), based on dose-related decrements in water and food consumption. Maternal body weight gain was significantly reduced at 1200 ppm, primarily during the first few days of treatment. Developmental NOEL = 200 ppm (vertebral malformation incidences of 0, 1, 3, and 0 in controls through increasing treatment groups, respectively). There were small (not statistically significant) decrements in fetal body weights at 600 and 1200 ppm, considered to be minor treatment effects. Study is acceptable. No adverse effects are indicated (the equivocal increase in vertebral malformations at 600 ppm lacked dose-response and was in the presence of marked maternal treatment response). Aldous, 1/5/01.

50288-055 114191 Duplicate copy of 50288-058 115606, above.

50288-065 130827 Irvine, L. F. H., "Sodium chlorite: rabbit teratology dose ranging study (drinking water administration)." Project ID CMA/2/R, 9/21/90. This was the pilot for study 50288-058 115606, above. Five does/group were dosed at 0, 200, 800, and 1200 on gestation days 7-19. Parameters included hematology at term for does. Fetuses were evaluated for reproduction indices and for external abnormalities. Female body weight, food consumption, and water consumption were sharply reduced at 800-1200 ppm. Hematology parameters appeared very modestly reduced at 1200 ppm only. There were no apparent treatment effects on fetuses. This study justifies selection of dosages for the primary study. Aldous, 1/5/01 (no worksheet).

GENE MUTATION

****50037-018 130832** Cifone, M. A., "Mutagenicity evaluation of chlorine dioxide in the mouse lymphoma forward mutation assay," Litton Bionetics, Inc., Kensington, MD, Oct., 1986. LBI Project No. 20989. Fischer L5178Y mouse lymphoma cells were tested with chlorine dioxide in a phosphate buffered saline solution (not otherwise described). Test cells were heterozygous for thymidine kinase expression, so that a single mutation in the functional gene could lead to a phenotype lacking thymidine kinase. Survivability in medium containing 5-trifluorothymidine (TFT) was taken as evidence of mutagenicity. Test cells were added at 3×10^6 cells/tube, with 10 ml medium/tube. Cells were exposed to test article for 4 hr, then washed twice prior to being suspended in a growth medium. After an expression period of 48 hr, aliquots were transferred to medium containing TFT. Colonies were counted after 10-14 days in this medium. Chlorine dioxide was tested at 1.3 to 24.3 $\mu\text{g/ml}$ without S9 and at 6.7 to 48.3 $\mu\text{g/ml}$ with S9 (higher levels were lethal in both cases). Mutant frequency was sufficiently elevated to constitute a positive response without S9 at treatment levels of 3.2 to 24.3 $\mu\text{g/ml}$ and in chlorine dioxide

medium with S9 at 48.3 µg/ml. Positive controls (EMS and 3-MCA) were used without and with S9, respectively. This study has several acknowledged deficiencies including no repeat trial, however it presents clear positive responses, consistent with several other mutagenicity studies of various types. This study is of sufficient quality to address the gene mutation data requirement. Aldous, 1/24/01.

CHROMOSOME EFFECTS

50288-018 130831 A copy of 50288-058 115602, previously reviewed (see above).

****50288-058 115603** Ivett, J. L., "Mutagenicity evaluation of chlorine dioxide in the mouse bone marrow cytogenetic assay," Litton Bionetics, Inc., June 1984. LBI Project No. 22202. CD-1 mice, 5/sex/group, were dosed with aqueous solutions of chlorine dioxide by ip injection, made from stock solutions of 4.25 or 3.92 mg/ml. Achieved dose levels were 0, 1.7, 5.2, or high dose of 15.4 to 16.1 mg/kg of chlorine dioxide. Positive control was triethylenemelamine (1.5 mg/kg). The latter was administered only at 24 hr before sacrifice, whereas other treatments were administered at 6 hr, 24 hr, and 48 hr before sacrifice. There were 5 mice/sex at each dose/treatment combination. Mice were administered 4 mg/kg colchicine 3 hr before sacrifice. Tibial marrow cells were collected, fixed, stained, coded, and scored (blind to treatment). Where possible, 50 spreads were read per mouse. Mitotic indices were also recorded. Various chromosome and chromatid aberrations were scored, however tables did not include chromatid gaps in summary indices. Chlorine dioxide did not elicit chromosomal aberrations. Positive control was functional. Acceptable, with no adverse effects. Aldous, 1/24/01.

50288-018 130829 A copy of 50288-058 115603, reviewed by DPR (see above)

50288-058 115604 Moore, M. R., "Evaluation of chlorine dioxide in the mouse dominant lethal assay," Litton Bionetics, Inc., Aug. 1984. LBI Project No. 22203. CD-1 mice, 12/group [15/group in the 20 mg/kg group] were dosed once intraperitoneally with chlorine dioxide (0, 2, 7, or 20 mg/kg, derived from stock solution at 2.9 mg/ml). A functional positive control group (triethylenemelamine, 0.3 mg/kg) was treated in parallel. Mice were mated weekly for 4 weeks, beginning 3 days after treatment. Mating was 1:2 M:F each week, and males were cohabited with females for 5 days, then rested for 2 days before the next mating. Females were necropsied 14 days after the midpoint of the mating week, and were examined for pregnancy and for numbers of living and dead implantations. Seven of the 15 high dose males died, and there were only 3 pregnant females during the first mating period after treatment in that group. Some mean values or indices differed from controls or other groups during that time in that group, although none were statistically significant. This sample was too small to interpret. This study is unacceptable and cannot be upgraded because (1) the protocol was limited to the last 4 weeks of the male spermatogenic cycle, and (2) there were too few females mated in all groups, and (3) there were too few pregnant females at week 1 to allow meaningful inferences, as indicated above. No adverse effect is indicated. Aldous, 1/24/01.

50288-018 130834 A copy of 50288-058 115604, previously reviewed (see above).

****50037-018 130833** Galloway, S. M. and J. L. Ivett, "Mutagenicity evaluation of chlorine dioxide in an in vitro cytogenetic assay measuring chromosomal aberration frequencies in Chinese hamster ovary (CHO) cells," Litton Bionetics, Inc., Kensington, MD, Oct., 1986. LBI Project No. 20990. The test

article was variously described as concentration of 2.227 mg/ml or 4.25 mg/ml. This material was supplied in phosphate buffered saline (PBS), which was used as the vehicle for dilutions. CHO-WBI cell line cultures of 1.5×10^6 cells per flask in exponential growth phase were exposed for 10 hr without S9 or for 2 hr with S9, and mitotic cells were harvested in both cases 12.5 hr after the onset of exposure. Colcemid was added 2.5 hr before harvest in both cases. In trials both with and without S9, 200 metaphase cells per treatment level were scored [also 100 cells per untreated control group and 100 cells per solvent (PBS) control], and treated group aberration frequencies were compared against combined controls. Sufficient positive controls were tested to validate technique (cyclophosphamide with S9 and Mitomycin C without S9). Results were clearly positive without S9 at 10 to 15 $\mu\text{g/ml}$, and with S9 at the highest dose level permitting cell survival (50 $\mu\text{g/ml}$). This study has several deficiencies with respect to guidelines, however it presents clear positive responses, consistent with several other mutagenicity studies of various types. This study is of sufficient quality to address the chromosomal aberrations data requirement. Aldous, 1/24/01.

DNA DAMAGE

50037-018 130828 Rundell, J. O. "Evaluation of chlorine dioxide in the in vitro transformation of Balb/3T3 cells assay," Litton Bionetics, Inc., Kensington, MD, Oct., 1986. LBI Project No. 20992. This procedure exposed cells of a clone which usually exists in monolayer conformation, to evaluate frequency of transformation of some cells to phenotypes which form foci consisting of cells of variable shapes which often stain darkly. Chlorine dioxide liquid (test article was not further characterized) was tested at 0 (water), 1, 2, 3, 5, or 6 $\mu\text{g/ml}$ starting concentration in at least 18 flasks per group. Tightly closed flasks were incubated for 72 hours with test article before cells were washed and then maintained for 4 weeks for expression of colonies of transformed cells. Chlorine dioxide concentrations spanned an effective exposure range based on cytotoxicity. The positive control (2.5 $\mu\text{g/ml}$ of 3-MCA) was functional. There was no indication of a treatment response to chlorine dioxide. This study is not acceptable as presented, and does not appear to be upgradeable, due to lack of characterization of the test article and of details of scoring of foci. Several additional concerns are also noted in this worksheet. Aldous, 1/24/01.

**50288-058 115602 Ivett, J. L., "Mutagenicity evaluation of chlorine dioxide in the sister chromatid exchange assay in vivo in mouse bone marrow," Litton Bionetics, Inc., July 1984. LBI Project No. 22204. Five ICR male mice/group were dosed with 0, 9, 21, 28, or 39 mg/kg chlorine dioxide (aqueous solution) intraperitoneally just after implantation with 50 mg BrdUrd. The positive control was 10 mg/kg cyclophosphamide. Colchicine was administered by subcutaneous injection 2 hr before sacrifice. Mice were killed 26 hr after treatment with test article. Marrow cells from tibiae were collected and processed for sister chromatid exchange evaluation. No increases in sister chromatid exchange occurred with chlorine dioxide. Cyclophosphamide was an effective positive control. Study was initially classified as unacceptable but upgradeable (needing justification for use of one sex only). A response letter from John DiLoreto on 8/21/01 noted that DPR Document No. 50288-017, Record No. 043602 had found males to be more sensitive than females to chlorite [the difference is negligible: oral LD50 values were 255 mg/kg (M) and 270 mg/kg (F)]. Necropsy observations were comparable between sexes in that study. The author of the response letter noted that males tend to be more sensitive than females to SCE responses. DPR has no database to confirm or refute this statement. Since test article is a simple inorganic oxidant, differential routes of metabolism between sexes would appear unlikely. The study can

be upgraded to acceptable. No adverse effect. Aldous, 12/12/00 and 9/10/01.

OTHER STUDY TYPES

****50288-058 115605** Ridgway, P., "Sodium chlorite: 13 week oral (gavage) toxicity study in the rat", Toxicol Laboratories Ltd., Herefordshire, 4/24/92. Laboratory Project ID # CMA/13/R. Fifteen Crl:CD®(SD)BR rats/sex/group were dosed by gavage with sodium chlorite (adjusted for 80.9% purity) at 0, 10, 25, or 80 mg/kg/day, 7 days/week in a standard subchronic study design. Subchronic NOEL = 10 mg/kg/day (primarily based on ulceration, hyperkeratosis, and/or chronic inflammation of the non-glandular stomach epithelium in 2 males at 25 mg/kg). Similar histopathology was found in both sexes at 80 mg/kg/day, along with reduced RBC counts, Hb, HCT, and elevated reticulocyte counts (some findings only in males). This dose presented some enlarged spleens, and low incidences of splenic extramedullary hematopoiesis, considered to be treatment-related. Clinical observations of "salivation" were reported in all 80 mg/kg/day rats. Four high dose rats died prematurely due to treatment: two of them having severe anemia. Study is acceptable, with no adverse effects (since findings were primarily limited to a comparatively high dose level of a compound expected to be irritating to exposed mucosae because it is an oxidant at a comparatively high pH). Aldous, 12/11/00.

50288-064 130826 (exact duplicate of 50288-058 115605, above)

MISCELLANEOUS SUMMARY REPORTS

50288-059 115608 A Chemical Manufacturers Association document with 17 tabbed sections occasionally referred to studies of potential interest to SB-950. Tab 4 provides a 1-page summary of an unspecified mouse oncogenicity study, which appears to be Kurokawa *et al.* (1986), based on similarity to the description of that study in Record No. 115609, below. Summary does not identify oncogenicity effects. There were no other noteworthy entries. Aldous, insufficient information to review, hence no worksheet, 1/8/01.

50288-059 115609 "A review of the uses, chemistry and health effects of chlorine dioxide and the chlorite ion," Chlorine Dioxide Panel of Chemical Manufacturers Association, April 1989. Pages 19-34 discuss several studies which relate to SB-950. Although nothing in this record is a full study, some conclusions are: (1) Chlorine dioxide and chlorite have the potential to cause methemoglobinemia and hemolytic anemia, (2) Chlorine dioxide oral doses in rat metabolism studies [non-enzymatic redox-type reactions] lead primarily to chloride ions, with much lesser amounts of chlorite, and very small amounts of ClO_3^- (chlorate) being excreted in urine (the major route of elimination), (3) Subchronic studies using African green monkeys indicated a transient reduction in thyroxine following doses of 100 ppm chlorine dioxide in drinking water, (4) Rabbits exposed to chlorine dioxide in air for 5 hr/day for 4 weeks at 2.5 to 10 ppm suffered bronchopneumonia and increased leukocyte counts. At the lowest dose tested in that study (2.5 ppm) there were only unspecified "reversible pulmonary lesions" detected. (5) A chronic rat drinking water study (duration of 11 months, by Allen and Jandle, 1960) found a number of changes which appear to have been subchronic or subacute in duration. Following treatment with 1, 10, 100, or 1000 mg/L of chlorine dioxide or 10 or 100 mg/L of chlorite, common signs were decreased blood glutathione, osmotic fragility of blood cells, decreased thymidine incorporation in liver and kidney tissues, and increased thymidine incorporation in intestinal mucosa. (6) Several kinds of genetic toxicity tests

were performed, and some of these were positive for chlorine dioxide or chlorite, including a mouse micronucleus test using either compound by the ip route. The micronucleus test was negative when chlorite was tested by oral dosing. (7) A drinking water mouse oncogenicity study by Kurokawa *et al.* using sodium chlorite (1986) was determined by investigators to be negative for oncogenicity. A re-analysis of data from the above study by Yokose *et al.* (1987) concluded that “clear evidence of carcinogenic activities of sodium chlorite in B6C3F1 mice was not observed.” (8) Water disinfected with unspecified amounts of chlorine dioxide was administered subcutaneously to Sencar mice, followed by application of phorbol myristate acetate (PMA) as a tumor promotor. Chlorine dioxide was stated to have been negative in this test (Bull *et al.*, 1980). (9) A developmental drinking water study by Suh *et al.* (1983) using chlorine dioxide at 0, 1, 10, or 100 ppm reported a decrement in total implants and live fetuses per dam at 100 ppm, but not at lower dose levels. (10) A non-standard reproduction study in Long-Evans rats by Carlton *et al.* (1987) found no changes in the reproductive parameters examined following treatment with 0, 1, 10, or 100 ppm of sodium chlorite (presumably in drinking water), however T3 and T4 in blood of 100 ppm pups was decreased (apparent NOEL = 10 ppm). (11) A reproduction study by Couri *et al.* (1982) used 0.1, 0.5, or 2.0% sodium chlorite in drinking water. The highest dose led to increased stillbirths and decreased litter size. All groups had reduced crown-rump lengths. No other responses were identified. (12) Female A/J mice were dosed with 0 or 100 ppm chlorite (in drinking water??) from mating through lactation [Moore and Calabrese (1982)]. Pup growth rates and weanling weights were reduced at 100 ppm. Taylor and Pfohl (1985) performed a study in which neonatal rats were exposed to chlorine dioxide either by gavage [14 mg/kg: age of pups exposed not specified, apparently a single dose] or indirectly via milk from dams drinking water with 2, 20, or 100 ppm chlorine dioxide. Gavage-treated pups and pups of dams treated at 100 ppm had decreased locomotor activity and decreased T4 in blood at day 21. Another component of this study suggested delayed locomotor development and reduced brain weights under unspecified treatment conditions. Clinical and epidemiological studies were also reviewed. None of these studies described briefly in this record would appear to address modern data requirements for chlorine dioxide or for chlorite. Aldous, 1/24/01 (no worksheet).

50288-018 130836 Cavagnaro, J. and B. H. Keech, “Cytotoxicity testing of biomaterials: agar-overlay screening assay,” Hazleton Biotechnologies Corp., 2/17/86, Project No. 2295-102. Ten polymers were treated with chlorine dioxide (6 hr, about 60 mg/L), then aerated for 18 hr prior to placement on agar overlaying Mouse Fibroblast L-929 cells. Cells were stained with neutral red dye prior to exposure to the 1 cm² polymer samples. Decoloration of stained monolayers under the samples represented cytotoxicity. Three trials were conducted. Two polymers were cytotoxic in this assay (Lexan 9440-112 and Lexan 9030-112). All other polymers were negative under study conditions. Study is not required under SB-950 and there is no DPR worksheet. Aldous, 1/24/01.

50288-018 130837 (primarily protocol for 50288-018 130836, above)

50288-059 115610 “Chlorine dioxide: drinking water issues.” Second International Symposium, Houston, TX, May, 1992. This record contains largely reproductions of overlays used in the symposium. The record describes physical characteristics of chlorine dioxide, processing techniques, worker safety information, and brief references to some laboratory animal studies. No worksheet. Aldous, 1/24/01.